



---

Year: 2013

---

## **Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6%) in severe burn injury: a randomized, controlled, double-blind clinical trial**

Béchir, Markus ; Puhan, Milo A ; Fasshauer, Mario ; Schuepbach, Reto A ; Stocker, Reto ; Neff, Thomas A

**Abstract:** **INTRODUCTION:** There are limited data on the efficacy of early fluid resuscitation with third generation hydroxyethyl starch (HES 130) in burn injury. Adverse effects of HES on survival and organ function have been reported. **METHODS:** In this randomized, controlled, double-blind trial 48 patients with severe burn injury were assigned to receive either Lactated Ringer's solution plus 6% HES 130/0.4 in a ratio of 2:1 or Lactated Ringer's solution with no colloid supplement for the first 72 hours. Primary outcome parameter was the group difference of administered total fluid from intensive care unit (ICU) admission up to day 3. Secondary outcomes included kidney and lung injury and failure, length of stay, and mortality. **RESULTS:** 3 days total of administered resuscitation fluid (medians) was 21,190 ml in the Lactated Ringer's group and 19,535 ml in the HES group (HES: -1,213 ml;  $P = 0.39$ ). Creatinine levels day 1 to 3 (HES: +0.4 mmol/l; 95% CI -18.7 to 19.5;  $P = 0.97$ ) and urinary output day 1 to 3 (HES: -58 ml; 95% CI -400 to 284;  $P = 0.90$ ) were not different. 6 patients in each group developed acute respiratory distress syndrome (ARDS) (risk ratio 0.96; 95% CI 0.35 to 2.64;  $P = 0.95$ ). Length of ICU stay (HES vs. Lactated Ringer's: 28 vs. 24 days;  $P = 0.80$ ) and length of hospital stay (31 vs. 29 days;  $P = 0.57$ ) were similar. 28-day mortality was 4 patients in each group (risk ratio 0.96; 95% CI 0.27 to 4.45;  $P = 0.95$ ), in-hospital mortality was 8 in the HES group vs. 5 patients in the Lactated Ringer's group (hazard ratio 1.86; 95% CI 0.56 to 6.19;  $P = 0.31$ ). **CONCLUSIONS:** There was no evidence that early fluid resuscitation with balanced HES 130/0.4 (6%) in addition to Lactated Ringer's solution would lead to a volume sparing effect in severe burn injury. Together with the findings that early renal function, incidence of ARDS, length of stay, and mortality were not negatively influenced by HES in this setting, balanced HES 130/0.4 (6%) plus Lactated Ringer's solution could not be considered superior to Lactated Ringer's solution alone. Trial registration: ClinicalTrials.gov NCT01012648.

DOI: <https://doi.org/10.1186/cc13168>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-87624>

Journal Article

Accepted Version

Originally published at:

Béchir, Markus; Puhan, Milo A; Fasshauer, Mario; Schuepbach, Reto A; Stocker, Reto; Neff, Thomas A (2013). Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6%) in severe burn injury: a randomized, controlled, double-blind clinical trial. *Critical Care*, 17(6):R299.

DOI: <https://doi.org/10.1186/cc13168>

This Provisional PDF corresponds to the article as it appeared upon acceptance. Copyedited and fully formatted PDF and full text (HTML) versions will be made available soon.

## **Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6%) in severe burn injury: a randomized, controlled, double-blind clinical trial**

*Critical Care* 2013, **17**:R299 doi:10.1186/cc13168

Markus Béchir (markus.bechir@paraplegie.ch)  
Milo A Puhan (milo.puhan@ifspm.uzh.ch)  
Mario Fasshauer (mario.fasshauer@usz.ch)  
Reto A Schuepbach (reto.schuepbach@usz.ch)  
Reto Stocker (reto.stocker@usz.ch)  
Thomas A Neff (thomas.neff@stgag.ch)

**ISSN** 1364-8535

**Article type** Research

**Submission date** 11 July 2013

**Acceptance date** 2 December 2013

**Publication date** 23 December 2013

**Article URL** <http://ccforum.com/content/17/6/R299>

This peer-reviewed article can be downloaded, printed and distributed freely for any purposes (see copyright notice below).

Articles in *Critical Care* are listed in PubMed and archived at PubMed Central.

For information about publishing your research in *Critical Care* go to

<http://ccforum.com/authors/instructions/>

# Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6 %) in severe burn injury: a randomized, controlled, double-blind clinical trial

Markus Béchir<sup>1,4,\*</sup>

Email: markus.bechir@paraplegie.ch

Milo A Puhan<sup>2</sup>

Email: milo.puhan@ifspm.uzh.ch

Mario Fasshauer<sup>1</sup>

Email: mario.fasshauer@usz.ch

Reto A Schuepbach<sup>1</sup>

Email: reto.schuepbach@usz.ch

Reto Stocker<sup>1</sup>

Email: reto.stocker@usz.ch

Thomas A Neff<sup>1,3</sup>

Email: thomas.neff@stgag.ch

<sup>1</sup> Surgical Intensive Care Medicine, University Hospital of Zurich, Raemistrasse 100, Zurich CH-8091, Switzerland

<sup>2</sup> Institute for Social and Preventive Medicine, University of Zurich, Zurich 8001, Switzerland

<sup>3</sup> Department of Anesthesia & Intensive Care Medicine, Cantonal Hospital of Muensterlingen, Muensterlingen 8596, Switzerland

<sup>4</sup> Swiss Paraplegic Center, Department of Intensive Care, Pain and Operative Medicine, Nottwil 6207, Switzerland

\* Corresponding author. Surgical Intensive Care Medicine, University Hospital of Zurich, Raemistrasse 100, Zurich CH-8091, Switzerland

## Abstract

### Introduction

There are limited data on the efficacy of early fluid resuscitation with third generation hydroxyethyl starch (HES 130) in burn injury. Adverse effects of HES on survival and organ function have been reported.

## Methods

In this randomized, controlled, double-blind trial 48 patients with severe burn injury were assigned to receive either Lactated Ringer's solution plus 6% HES 130/0.4 in a ratio of 2:1 or Lactated Ringer's solution with no colloid supplement for the first 72 hours. Primary outcome parameter was the group difference of administered total fluid from intensive care unit (ICU) admission up to day 3. Secondary outcomes included kidney and lung injury and failure, length of stay, and mortality.

## Results

3 days total of administered resuscitation fluid (medians) was 21,190 ml in the Lactated Ringer's group and 19,535 ml in the HES group (HES: -1,213 ml;  $P = 0.39$ ). Creatinine levels day 1 to 3 (HES: +0.4  $\mu\text{mol/l}$ ; 95% CI -18.7 to 19.5;  $P = 0.97$ ) and urinary output day 1 to 3 (HES: -58 ml; 95% CI -400 to 284;  $P = 0.90$ ) were not different. 6 patients in each group developed acute respiratory distress syndrome (ARDS) (risk ratio 0.96; 95% CI 0.35 to 2.64;  $P = 0.95$ ). Length of ICU stay (HES vs. Lactated Ringer's: 28 vs. 24 days;  $P = 0.80$ ) and length of hospital stay (31 vs. 29 days;  $P = 0.57$ ) were similar. 28-day mortality was 4 patients in each group (risk ratio 0.96; 95% CI 0.27 to 4.45;  $P = 0.95$ ), in-hospital mortality was 8 in the HES group vs. 5 patients in the Lactated Ringer's group (hazard ratio 1.86; 95% CI 0.56 to 6.19;  $P = 0.31$ ).

## Conclusions

There was no evidence that early fluid resuscitation with balanced HES 130/0.4 (6%) in addition to Lactated Ringer's solution would lead to a volume sparing effect in severe burn injury. Together with the findings that early renal function, incidence of ARDS, length of stay, and mortality were not negatively influenced by HES in this setting, balanced HES 130/0.4 (6%) plus Lactated Ringer's solution could not be considered superior to Lactated Ringer's solution alone.

## Trial registration

ClinicalTrials.gov NCT01012648

## Introduction

There is an ongoing debate on fluid resuscitation in severe burn injury, especially for the first 24 hours after trauma. Aggressive intravenous fluid therapy according to the Baxter formula is a mainstay of initial therapy. Multiple pathophysiological changes characterize the early posttraumatic phase. Massive systemic inflammation comparable to severe sepsis leads by the release of numerous mediators such as leukotrienes, prostaglandins and particularly histamine, in combination with complement activation products, to an extensive capillary leak [1,2]. Intravascular molecule and fluid shifts into the extravascular space cause severe hypovolemia and shock [3]. Changes in capillary membrane permeability also produce electrolytic alteration with intracellular sodium accumulation and consecutive cellular swelling [4]. Excessive tissue oedema, promoted to a large extent by the leakage of plasma proteins into the extravascular space normally occurs within the first few hours after trauma. The capillary leak is believed to resolve within 8 to 24 hours after trauma, but data vary [1,5].

In this critical situation of massive inflammation, hypovolemia and large oedema formation, it still remains unclear whether a “crystalloid only” therapy or a combination of crystalloids plus colloids should be used for volume resuscitation. Expert opinion consisted of strictly avoiding colloids such as hydroxyethyl starches (HES) during the first 24 hours [6]. This restriction was based on reports from the early 1970s expressing the fear of overloading the interstitial compartment with colloids in the early stage of trauma due to increased capillary leakage, thus leading to impaired wound healing after surgical treatment [7,8]. Although the Cochrane Injuries Group presented in 1998 a relative risk of death after albumin administration of 2.4 in a meta-analysis [9], human albumin is still used in burn aiming to reduce the fluid requirements for resuscitation [10,11] and tissue oedema. With the same intention different types of HES are frequently administered in burn injury, although safety and efficacy of HES products for fluid resuscitation is not fully evaluated and is intensely disputed especially during the last few years. However, we just recently have demonstrated in a prospective interventional open label study that hyperoncotic HES 200/0.5 (10%) might be associated with fatal outcome when used for early fluid resuscitation in severe burn injury [12]. A recent randomized controlled trial assigned 26 burn patients to either Hartmann’s solution plus HES 200/0.6 (6%) or to Hartmann’s solution only. The HES-supplemented fluid therapy led to significantly less fluid application than the Hartmann’s regimen and showed reduced interstitial oedema [13]. The least side effects on kidney function and coagulation is attributed to the third generation hydroxyethyl starches such as HES 130/0.4 (6%), but data on early fluid resuscitation in major burn with these modern starches are limited.

We therefore addressed in this current RCT the question whether modern HES 130/0.4 (6%) administered within the first 24 hours after severe burn injury and up to 72 hours of treatment would be able to show any fluid sparing effect.

(ClinicalTrials.gov number, NCT01012648)

## **Materials and methods**

### **Trial design**

This study was an investigator-initiated, prospective, randomized, controlled, double-blind single-center trial. The study protocol was approved by the local ethical committee (KEK 4, Canton Zurich) and the Swiss Agency for Therapeutic Products (Swissmedic). Power calculation and planning of the statistical analysis was done at the Horten Centre for patient-oriented research, University Hospital of Zurich. Reporting of the study was done according to the CONSORT guidelines.

### **Participants**

All adults (age  $\geq 16$  yrs) with 2nd or 3rd degree acute burn injury and more than 15% of body surface area (BSA) burned who admitted to the University Hospital of Zurich burn unit between November 1, 2009 and January 31, 2013 were eligible for the study. All necessary written informed consent (deferred consent, if necessary, according to Swiss law HMG § 55 and §56) was obtained from the patient or their legal surrogate within 24 hours after inclusion. In the case of written consent of the legal surrogate, all survivors gave written informed consent after recovery, which is in line with the local ethical committee regulations. Patients were excluded when they were expected to succumb within the next 24 to 36 hours,

i.e. burn victims with whole body burn trauma, or in situations of palliative care, pregnancy, lack of informed consent, known allergy to HES, contraindications for balanced 6% HES 130/0.4, intracerebral bleeding, acute renal failure, severe hyponatremia and other severe electrolyte disorders, severe von Willebrand Syndrome and acute liver failure.

## **Study setting**

The study was performed in a tertiary burn unit at the university hospital of Zurich, Switzerland. The center is the larger of the two national burn units in Switzerland, running 6 acute care beds. Approximately 80 severe burn victims are admitted to the university hospital per year.

## **Interventions**

The primary study medication was balanced 6% HES 130/0.4. After patient enrollment and randomization, fluid resuscitation was done as follows. Each patient first received 2 bags of unblinded Lactated Ringer's solution (500 ml each bag), followed by 1 bag (500 ml) of blinded study solution, the latter being either again Lactated Ringer's solution or balanced 6% HES 130/0.4. After each bag of study solution, all patients received again 2 bags of unblinded Lactated Ringer's solution, before a next bag of study solution from the blinded box was infused. This fluid regimen alternating unblinded Lactated Ringer's fluid with blinded study solution assured an overall ratio of crystalloids versus colloids of 2:1 in the HES patients. The patients not receiving HES but blinded Lactated Ringer's study solution instead were exposed solely to crystalloids during the entire course of the study. Fluid resuscitation was guided by predefined target variables as listed in Figure 1 (see supplements). Accordingly, fluid administration was increased or decreased until target variables were reached. The administration of additional albumin or any other colloid was excluded in both the groups. All resuscitation fluids were administered as continuous infusions via peristaltic pumps. Infusion rate (ml/h) was continuously adjusted to the actual patient fluid needs. Except for volume resuscitation there was no difference in patient care including cardiovascular monitoring, pharmacologic and respiratory support, nutrition, and surgical treatment of burn wounds.

---

**Figure 1** MAP represents mean arterial pressure, ScvO<sub>2</sub> central venous oxygen saturation, UO urinary output, Hct hematocrit, respectively.

---

## **Outcome measures**

Primary outcome was the group difference of administered resuscitation fluid within the first 72 hours after admission. Secondary endpoints were creatinine level at day 1 and the difference over day 1 to 3, urine output at day 1 and the difference over day 1 to 3, incidence of ARDS [14] during hospitalization, length of stay in the ICU, length of stay in the hospital, inhospital mortality, and 28-day mortality. Collected baseline characteristics were age, sex, systolic and diastolic blood pressure, heart rate, body weight, body height, percentage of burn, and the amount of prehospital administered fluids.

A post-hoc analysis was performed for 90-day mortality and incidence of renal replacement therapy (RRT) during hospital stay.

## Sample size

We based our sample size calculations on the primary outcome, which is the total volume of fluids given within the first 72 hours of treatment. We used data from our previous study with HES 200/0.5 [12] to estimate the average total volume of fluids given within the first 72 hours of treatment with crystalloids (25 liters with crystalloid and 18 liters with HES) and to estimate its variability (standard deviation of around 12 and 7 liters, respectively). A sample size of 24 patients in each group allowed showing a difference of 25%, respectively in total volume of fluids given within the first 72 hours of treatment between the groups with a power of 80% at a significance level of 5% (two-sided).

## Blinding and randomization

A third party not involved in the conduction (KAZ, Kantonsapotheke, Zürich) performed randomization and prepared the study solution, either balanced 6% HES 130/0.4 or Lactated Ringer's solution, by sealing the identical 500 ml bags in black plastic foil concealing the product label and content. Thus, there was no possibility to recognize the fluid used. Bags were packed into boxes. 3 boxes of the same content labelled in consecutive order were assigned to each patient, one box for each 24 hours period up to 72 hours. For randomization, minimization was used with stratification for age ( $<50$  or  $\geq 50$  years). Since minimization does not have a prespecified randomization list, concealment of random allocation was ensured. Thus, all patients were randomized double blind either to the Lactated Ringer's *plus* balanced 6% HES 130/0.4 group or to the Lactated Ringer's only group, respectively, and study medication was assigned to the patients. To make sure, that there was no overload of 6% HES 130/0.4 study medication, the maximum amount (for HES according to the manufacturer's manual 50 ml per kg BW per 24 hours) was calculated based on the estimated body weight at study enrollment. A body weight of 80 kg e.g. led to 4'000 ml of study solution, which resulted in 8 bags of 500 ml each of blinded solution. Not more than that was brought to the patient.

## Statistical methods

We included all patients in the analysis according to the group they were randomized to. To compare the outcomes between the two groups we used linear regression analysis for continuous outcomes (e.g. fluids), logistic regression for binary outcomes (e.g. ARDS) and Cox proportional hazard regression for in-hospital mortality, always with group allocation as independent variable. To compare the total volume of fluids given within the first three days after randomization, creatinine values, and urinary output over the first 72 hours, we used a random effects model that took the auto-correlated structure of repeated measurements (measurement on first, second and third day) into consideration (xtreg command of STATA). All analyses were conducted using STATA (STATA for Windows, version 10.2, Stata Corp; College Station, TX).

## Results

### Participants

From November 1, 2009 through January, 31 2013, 159 patients were assessed for inclusion into the study, 111 patients were not eligible. From the enrolled 48 patients, 23 patients were

assigned to receive Lactated Ringer's solution *plus* balanced 6% HES 130/0.4 (HES group) and 23 to receive Lactated Ringer's solution (Lactated Ringer's group). 2 patients had to be excluded from the study because they retrospectively did not fulfill inclusion criteria (1 primarily included patient with negative pregnancy test had to be excluded secondarily because of revised pregnancy test to positive shortly thereafter. 1 patient was initially assessed 20% deep burned area but showed less than 15% intraoperatively). 1 patient was lost for analysis in the Lactated Ringer's group because of early discharge within less than <72 hours from the ICU. This patient was formally not excluded, but no study data were available for incorporation into the statistics. Participant flow is shown in Figure 2. Baseline characteristics were well balanced between groups (Table 1).

---

**Figure 2 Study Flow Diagram.**

---

**Table 1 Baseline characteristics of the patients**

Characteristic	HES (N = 23)	Lactated Ringer's (N = 22)
Age (yrs)	49 (22, 69)	47 (26, 61)
Sex (male)	17 (73.9%)	17 (77.2%)
Systolic blood pressure (mmHg)	109 (93, 130)	123 (104, 150)
Diastolic blood pressure (mmHg)	60 (55, 65)	68 (59, 76)
Heart rate (beats/min)	83 (70, 95)	86 (75, 95)
Weight (kg)	75 (70, 83)	80 (70, 80)
Height (cm)	175 (170, 180)	176 (170, 180)
Burned TBSA (%)	31 (21, 47)	32 (20, 50)

Data are represented as median (25<sup>th</sup> and 75<sup>th</sup> percentile) *or* median (percent). None of the differences between the two groups were significant (P > 0.05).

Two patients were excluded although randomized because did not fulfill inclusion criteria and 1 patient was not excluded formally but was not in analyses because of lack of data.

TBSA represents total body surface area.

## Fluid therapy

During the pre-hospital phase the Lactated Ringer's group received a median of 1'800 ml and the HES group 2'000 ml of fluid, respectively (difference not significant); no colloids were administered. Calculated fluid requirement for the first 24 hours based on the Baxter formula was not different between the 2 groups (Lactated Ringer's group: 8'520 vs. HES: 9'000 ml). The median 3 days total of effectively administered fluid was 21'190 ml in the Lactated Ringer's group vs. 19'535 ml in the HES group. A median amount of 5'650 ml of HES was administered in the colloid group, no HES was administered in the Lactated Ringer's group (details see Table 2).



**Table 2 Fluid therapy**

Variable	HES (N = 23)	Lactated Ringer's (N = 22)
Prehospital crystalloids (ml)	2000 (1000, 2500)	1800 (1000, 3600)
Prehospital colloids (ml)	0 (0, 0)	0 (0, 0)
Baxter formula (ml)	9000 (5880, 13536)	8520 (7920, 18080)
Total fluids day 1 (ml)	10050 (6700, 16800)	11575 (9300, 19770)
Total fluids day 2 (ml)	5500 (3750, 8825)	5025 (3180, 9300)
Total fluids day 3 (ml)	3340 (2060, 7000)	4150 (1640, 6100)
Total fluids days 1–3 (ml)	19535 (13820, 29770)	21190 (14760, 33960)
Total crystalloids days 1–3 (ml)	13200 (10075, 19020)	21190 (14760, 33960)
Total colloids days 1–3 (ml)	5650 (3745, 9000)	0 (0, 0)

Data are represented as median (25<sup>th</sup> and 75<sup>th</sup> percentile).

## Outcomes

Regarding the primary endpoint there was a group difference in fluids given over the first 72 hours of -1'213 ml in the HES group, which was not statistically significant (95% CI -3'975 to 1'549;  $p = 0.39$ ). With regard to secondary outcomes there was no difference over the first 72 hours in creatinine levels ( $+0.4 \mu\text{mol/l}$ ; 95% CI -18.7 to 19.5;  $p = 0.97$ ) and in urinary output (-58 ml; 95% CI -400 to 283;  $p = 0.90$ ). The incidence of ARDS was 6 patients in each group (risk ratio 0.96; 95% CI 0.35 to 2.64;  $p = 0.95$ ) and there was again no difference in length of ICU stay and hospital stay (28 vs. 24 days;  $p = 0.80$  and 31 vs. 29 days;  $p = 0.57$ ), respectively. 28-day mortality was 4 patients in each group (risk ratio 0.96; 95% CI 0.27 to 4.45;  $p = 0.95$ ) and in-hospital mortality was 8 in the HES group vs. 5 in the Lactated Ringer's group (hazard ratio 1.86; 95% CI 0.56 to 6.19;  $p = 0.31$ ), see Table 3.

**Table 3 Primary and secondary outcomes**

Outcome	HES (N = 23)	Lactated Ringer's (N = 22)	Difference	P value
<b>Primary outcome</b>				
Total volume days 1–3 (ml)			–1213 (95%CI –3975 to 1549)	0.39
<b>Secondary outcomes</b>				
Creatinine day 1 (μmol/l)	77 (66, 99)	74 (55, 90)		
Creatinine days 1–3 (μmol/l)			0.4 (95% CI –18.7 to 19.5)	0.97
Urinary output day 1 (ml/d)	1360 (1020, 1770)	1430 (970, 2225)		
Urinary output days 1–3 (ml)			–58 (95% CI –400 to 283)	0.90
Incidence ARDS	6 (26.1%)	6 (27.3%)		
Risk ratio for ARDS with HES			0.96 (95% CI 0.35 to 2.64)	0.95
28-day mortality	4 (17.4%)	4 (18.2%)		
Risk ratio for 28-day mortality with HES			0.96 (95% CI 0.27 to 4.45)	0.95
In hospital mortality	8 (34.8%)	5 (22.7%)		
Hazard ratio for in-hospital death with HES			1.86 (95% CI 0.56 to 6.19)	0.31
Length of stay ICU (days)	28 (10, 58)	24 (11, 49)		0.80
Length of stay hospital (days)	31 (18, 58)	29 (14, 61)		0.57

Data are represented as median (25<sup>th</sup> and 75<sup>th</sup> percentile) *or* number of patients (percent) *or* risk ratio (confidence interval) *or* hazard ratios (confidence interval). For total volume, creatinine, and urinary output over days 1–3, absolute values with original units (confidence interval) are depicted.

The results of the post-hoc analysis of 90-day mortality and incidence of renal replacement therapy showed no difference between the groups. Data are depicted in Table 4.

**Table 4 Post-hoc analysis 90-day mortality and need for renal replacement therapy (RRT)**

Outcome (post-hoc analysis)	HES (N = 23)	Lactated Ringer's (N = 22)	Difference	P value
90-day mortality	8 (34.8%)	6 (27.3%)		
<b>Risk ratio</b> for 90-day mortality with HES			1.27 (95% CI 0.51 to 3.26)	0.59
Need for RRT	6 (26.1%)	6 (27.3%)		
<b>Risk ratio</b> for need of RRT with HES			0.96 (95% CI 0.35 to 2.64)	0.95

Data are represented as number of patients (percent) or risk ratio (confidence interval).

## Discussion

In this randomized, controlled trial no fluid saving effect was detected by the use of balanced 6% HES 130/0.4 as compared to Lactated Ringer's solution alone in patients with severe burn injury. Furthermore, early renal function as determined by serum creatinine levels, development of ARDS, length of ICU and hospital stay, in-hospital and 28-day mortality were not different between treatment groups.

In severe burn injury with massive systemic inflammation comparable to severe sepsis, aggressive fluid resuscitation to maintain hemodynamic stability and stable kidney function is pivotal. The most widely accepted formula to estimate fluid requirements in burns is the Baxter formula, which is, however, rather underestimating the volume needed in about half of the patients [15–17]. The downside of significant fluid load in burned patients might be

accentuated oedema formation and thus impaired wound healing after surgical treatment. Hence, a reduction of fluid load especially during the first 24 to 48 hours, where the most resuscitation volume is needed, appears to be desirable in order to improve surgical outcome.

The role of hydroxyethyl starch in various clinical settings remains controversial. A possible volume sparing effect, assigned to colloids in general, is the main indication for its widespread use, although the extent of fluid load reduction may be overestimated. There is only few data about the use of hydroxyethyl starch in patients with burn injury. Vlachou et al. showed in a recent randomized controlled trial in burned patients a clear volume sparing effect and furthermore reduced oedema formation with HES 200/0.6 (6%) supplementation [14]. However, as reported by our group, older generation HES such as the hyperoncotic HES 200/0.6 (10%) might be associated with higher incidence of renal failure and higher overall mortality in severe burn injury [12]. One explanation could be related to the fact, that only about 33 to 66% of the administered hyperoncotic HES is excreted in the urine in the first 24 hours after infusion [18]. Thus, the remaining HES molecules, which are still in high concentration, may circulate for a long time and a substantial proportion might accumulate in various tissues including kidney. Hyperoncotic HES deposition was demonstrated in dogs by histopathology in intravascular and interstitial spaces of various organs including proximal renal tubular cells, thus possibly inducing renal failure [19]. There are also many case studies describing acute deterioration of preexisting renal impairment after the administration of hyperoncotic HES [20,21].

Very limited data are available on modern third generation hydroxyethyl starches such as HES 130 in burns. Only one small randomized open label study reported more favourable parameters related to the extent of tissue oedema and a reduced mortality with HES 130/0.4 [13]. With regard to kidney function, James et al. just recently demonstrated in penetrating trauma patients resuscitated with HES 130/0.4 a better lactate clearance and less acute kidney injury than in patients treated with saline [22]. Furthermore, Boussekey and colleagues showed in a observational retrospective study in 363 ICU patients no difference in acute kidney injury after the use of HES 130/0.4 as compared to crystalloids [23]. These findings, not necessarily connecting the administration of HES 130/0.4 to acute renal failure, are supporting our current data showing no increasing creatinine levels over the first 3 days of fluid resuscitation with HES 130. However, it has to be mentioned, that in our study HES 130 was co-infused together with Lactated Ringer's solution in a ratio of 2:1, which might be protecting the kidney from acute deterioration and failure. In large contrast, several recent trials and analyses not focusing on burn injury have drawn different conclusions with regard to kidney failure. Although an improvement of sublingual microcirculation after resuscitation with HES 130/0.4 versus saline was reported [24], septic patients receiving HES 130 were more likely to developing acute kidney injury, requiring renal replacement therapy, and being at increased risk of death after 90 days [17,25]. This is in line with the findings in a large multicentre trial where it was shown in 7'000 patients that the application of HES 130/0.4 resulted in more adverse events and more renal replacement therapies as compared to patients receiving 0.9% saline for fluid resuscitation [26]. Taken this recent large studies and meta-analyses together, HES products including HES 130 preparations might be associated with increased mortality and acute kidney injury in ICU patients [27-32]. Whether this data can ultimately be translated to burn injury needs further investigation.

The current study has several limitations: *firstly*, the application of resuscitation fluids was algorithm based and conducted by different individuals of our ICU staff. Nevertheless, over two years of study duration, this effect has probably been levelled out over time. *Secondly*,

the used volume resuscitation algorithm was very traditional and did not include any hemodynamic measurement tools such as pulmonary artery catheter or PiCCO. Only clinical signs and various hemodynamic and surrogate parameters (mean arterial pressure, central venous oxygen saturation, urinary output, hematocrit) were used to guide volume therapy. The reason for this simplified approach comes on the one hand from our clinical experience with fluid therapy in burned patients suggesting that this approach is reliable, and on the other hand from the lack of clear evidence for better fluid therapy by the use of advanced hemodynamic guidance tools. Our data show that estimated fluid requirements for the first 24 hours (calculated with the Baxter formula) is comparable with the effectively infused amount of resuscitation fluid in both the HES and the crystalloid group. And as known from the literature, the Baxter formula rather underestimates the necessary amount of infusion fluid [15-17], which was the case in our study as well. *Thirdly*, power calculation was done to detect a potential volume sparing effect, but not to determine differences in mortality, organ failure and length of stay. The latter are secondary endpoints, for which the study is underpowered due to the relatively small sample size. Therefore, differences in mortality, organ failure and length of stay have to be interpreted with caution.

The strength of the study is it's randomized, double blinded and controlled design making the findings reliable and of clinical relevance. An implication for further research would be the initiation of randomized controlled trials with large sample sizes to strengthen the current evidence of a missing volume sparing effect of modern hydroxyethyl starches in burn injury. With regard to safety concerns that have arisen after the latest metaanalysis reporting a significant risk for mortality and acute kidney injury in various patient groups [28], further studies should specifically address this issue in burned patients.

## Conclusions

This randomized, controlled, double-blind study did not provide any evidence that early fluid resuscitation with balanced HES 130/0.4 (6%) as an add-on fluid to Lactated Ringer's solution during the first 72 hours after burn injury would lead to a volume sparing effect. Together with the findings that early renal function, incidence of ARDS, length of stay, and mortality were not negatively influenced by HES in this setting, balanced HES 130/0.4 (6%) plus Lactated Ringer's solution could not be considered superior to Lactated Ringer's solution alone.

## Key messages

- All patients received more resuscitation fluid than Baxter formula suggested.
- The use of balanced 6% HES 130/0.4 did not result in reduced fluid requirement in severe burn victims.
- There is no advantage of using 6% HES 130/0.4 in severe burn injury.

## Abbreviations

ARDS, Acute respiratory distress syndrome; HES, Hydroxyethyl starch; ICU, Intensive care unit; KEK, Kantonale Ethik Kommission [Cantonal Ethical Committee]

## Competing interests

TAN and RS have occasionally been participants of Fresenius Kabi and B. Braun nutrition and fluid therapy advisory board meetings and have received travel and accommodation support and also limited honorarium. MB has received travel and accommodation support and also limited honorarium (Fresenius Kabi and B. Braun). MF, MAP and RAS have no competing interests.

## Authors' contributions

RAS and MF collected the majority of the data and drafted parts of the manuscript. MAP performed statistical analysis. RS helped analyzing and interpreting the data and drafted parts of the manuscript. MB and TAN led the project, collected parts of the data, performed additional statistical analysis and drafted major parts of the manuscript. All authors read and approved the final manuscript.

## Funding

This study was supported by a grant from Fresenius Kabi, Stans, Switzerland, the manufacturer of balanced HES 130/0.4 (6%); Fresenius Kabi also supplied the study fluids. The funders had no input into, or control over, study design, data acquisition, data analysis and interpretation, nor on the writing of the manuscript.

## References

1. Pitt RM, Parker JC, Jurkovich GJ, Taylor AE, Curreri PW: **Analysis of altered capillary pressure and permeability after thermal injury.** *J Surg Res* 1987, **42**:693–702.
2. Youn YK, LaLonde C, Demling R: **The role of mediators in the response to thermal injury.** *World J Surg* 1992, **16**:30–36.
3. Warden GD: **Burn shock resuscitation.** *World J Surg* 1992, **16**:16–23.
4. Yowler CJ, Fratianne RB: **Current status of burn resuscitation.** *Clin Plast Surg* 2000, **27**:1–10.
5. Cocks AJ, O'Connell A, Martin H: **Crystalloids, colloids and kids: a review of paediatric burns in intensive care.** *Burns* 1998, **24**:717–724.
6. Holm C: **Resuscitation in shock associated with burns. Tradition or evidence-based medicine?** *Resuscitation* 2000, **44**:157–164.
7. Baxter CR: **Fluid volume and electrolyte changes of the early postburn period.** *Clin Plast Surg* 1974, **1**:693–703.
8. Baxter CR, Marvin JA, Curreri PW: **Early management of thermal burns.** *Postgrad Med* 1974, **55**:131–139.

9. **Human albumin administration in critically ill patients: systematic review of randomised controlled trials.** Cochrane Injuries Group Albumin Reviewers. *BMJ* 1998, **317**:235–240.
10. Ennis JL, Chung KK, Renz EM, Barillo DJ, Albrecht MC, Jones JA, Blackburne LH, Cancio LC, Eastridge BJ, Flaherty SF, *et al*: **Joint Theater Trauma System implementation of burn resuscitation guidelines improves outcomes in severely burned military casualties.** *J Trauma* 2008, **64**:S146–S151. discussion S151-142.
11. Wharton SM, Khanna A: **Current attitudes to burns resuscitation in the UK.** *Burns* 2001, **27**:183–184.
12. Bechir M, Puhon MA, Neff SB, Guggenheim M, Wedler V, Stover JF, Stocker R, Neff TA: **Early fluid resuscitation with hyperoncotic hydroxyethyl starch 200/0.5 (10%) in severe burn injury.** *Crit Care* 2010, **14**:R123.
13. Vlachou E, Gosling P, Moiemmen NS: **Hydroxyethylstarch supplementation in burn resuscitation—a prospective randomised controlled trial.** *Burns* 2010, **36**:984–991.
14. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R: **he American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination.** *Am J Respir Crit Care Med* 1994, **149**:818–824.
15. Cancio LC, Chavez S, Alvarado-Ortega M, Barillo DJ, Walker SC, McManus AT, Goodwin CW: **Predicting increased fluid requirements during the resuscitation of thermally injured patients.** *J Trauma* 2004, **56**:404–413. discussion 413–404.
16. Cartotto RC, Innes M, Musgrave MA, Gomez M, Cooper AB: **How well does the Parkland formula estimate actual fluid resuscitation volumes?** *J Burn Care Rehabil* 2002, **23**:258–265.
17. Friedrich JB, Sullivan SR, Engrav LH, Round KA, Blayney CB, Carrougner GJ, Heimbach DM, Honari S, Klein MB, Gibran NS: **Is supra-Baxter resuscitation in burn patients a new phenomenon?** *Burns* 2004, **30**:464–466.
18. Jungheinrich C, Scharpf R, Wargenau M, Bepperling F, Baron JF: **The pharmacokinetics and tolerability of an intravenous infusion of the new hydroxyethyl starch 130/0.4 (6%, 500 mL) in mild-to-severe renal impairment.** *Anesth Analg* 2002, **95**:544–551. table of contents.
19. Thompson WL, Fukushima T, Rutherford RB, Walton RP: **Intravascular persistence, tissue storage, and excretion of hydroxyethyl starch.** *Surg Gynecol Obstet* 1970, **131**:965–972.
20. De Labarthe A, Jacobs F, Blot F, Glotz D: **Acute renal failure secondary to hydroxyethylstarch administration in a surgical patient.** *Am J Med* 2001, **111**:417–418.

21. Waldhausen P, Kiesewetter H, Leipnitz G, Scielny J, Jung F, Bambauer R, von Blohn G: **Hydroxyethyl starch-induced transient renal failure in preexisting glomerular damage.** *Acta Med Austriaca* 1991, **18**:52–55.
22. James MF, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS: **Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma).** *Br J Anaesth* 2011, **107**:693–702.
23. Boussekey N, Darmon R, Langlois J, Alfandari S, Devos P, Meybeck A, Chiche A, Georges H, Leroy O: **Resuscitation with low volume hydroxyethylstarch 130 kDa/0.4 is not associated with acute kidney injury.** *Crit Care* 2010, **14**:R40.
24. Dubin A, Pozo MO, Casabella CA, Murias G, Palizas F Jr, Moseinco MC, Kanoore Edul VS, Palizas F, Estenssoro E, Ince C: **Comparison of 6% hydroxyethyl starch 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal-directed therapy of septic patients.** *J Crit Care* 2010, **25**:659. e651-658.
25. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, Madsen KR, Moller MH, Elkjaer JM, Poulsen LM, *et al*: **Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis.** *N Engl J Med* 2012, **367**:124–134.
26. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, *et al*: **Hydroxyethyl starch or saline for fluid resuscitation in intensive care.** *N Engl J Med* 2012, **367**:1901–1911.
27. Hartog CS, Kohl M, Reinhart K: **A systematic review of third-generation hydroxyethyl starch (HES 130/0.4) in resuscitation: safety not adequately addressed.** *Anesth Analg* 2011, **112**:635–645.
28. Zarychanski R, A-SAMTAF, *et al*: **Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis.** *JAMA* 2013, **309**:678–688.
29. Perel P, Roberts I, Ker K: **Colloids versus crystalloids for fluid resuscitation in critically ill patients.** *Cochrane Database Syst Rev* 2013, **2**:CD000567.
30. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S: **Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy.** *Intensive Care Med* 2013. DOI. 10.1007/s00134-013-2840-0.
31. Haase N: **Systematic review not influenced by Boldt's work.** *BMJ* 2013, **346**:f2280.
32. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, Wetterslev J: **Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis.** *BMJ* 2013, **346**:f839.

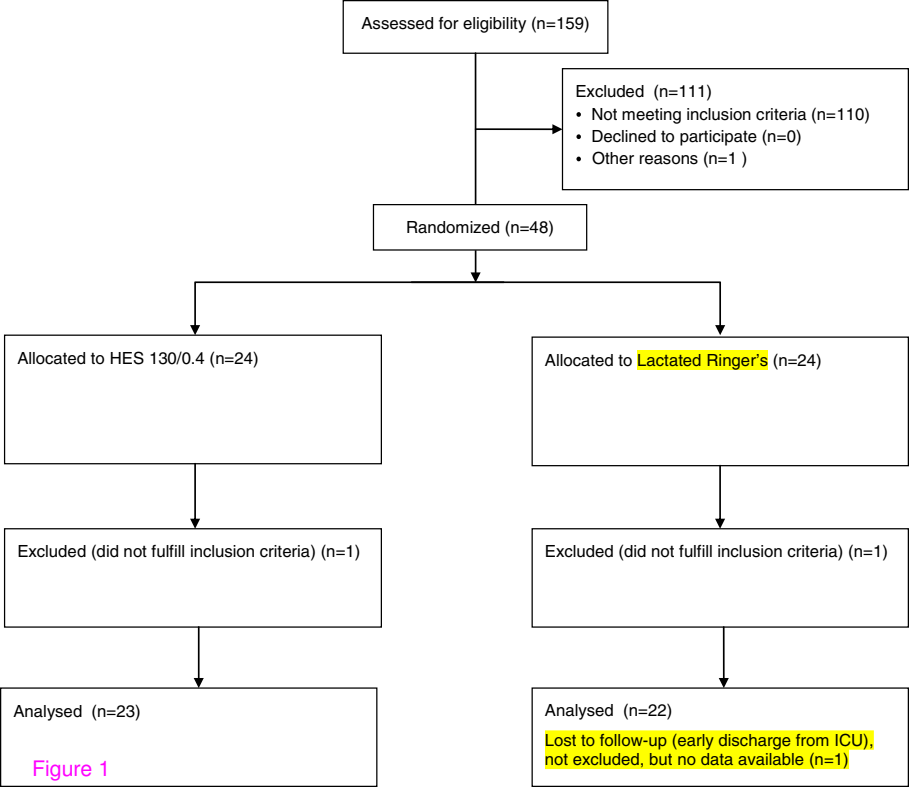


Figure 1



## **Continue fluid resuscitation, when :**

**1.                      MAP < 60 mmHg**

**or**

**2.                      ScvO<sub>2</sub> < 65%**

**or**

**3.                      UO < 0.5ml/kg**

**or**

**4.                      Hct > 55%**

- If the points 2 to 4 are fulfilled, but not point 1, start vasopressor therapy.**
- If the points 1 to 4 are fulfilled, reduce fluid resuscitation**